

cause of the high boiling point of the alcohols, the reaction temperature was held between 150 and 170°. A higher temperature caused decomposition.

Phenyloxy- and *p*-hydroxyphenyloxycaffeine were prepared by adding 1 mole of metallic sodium to slightly more than 2 moles of the phenol in a xylene solution and then 1 mole of 8-chlorocaffeine. The mixture was refluxed for five hours. In a second method, these two ethers were prepared by using the same proportions of reagents in an ethyl alcohol solution. The products were separated in the same manner as were the alkyl ethers. In the first procedure the xylene filtrate was distilled under reduced pressure to a small volume in order to secure a second crop of crystals. These methods differed from those of Baumann,<sup>6</sup> who used potassium hydroxide in an alcohol solution.

The last four ethers (table), containing phenyl groups, were most successfully recrystallized from 95% or dilute (40–50%) alcohol.

All of the caffeine ethers gave the murexide reaction. However, the phenyl derivatives gave a brick-red color instead of the usual bright red or scarlet. The stability of the ether-caffeine derivatives toward alkalis proved to be much greater than caffeine or most of the uric acid derivatives. Hot dilute hydrochloric acid readily converted all of the alkyl ethers to hydroxycaffeine. The same compound was formed when the ethers were heated alone at

temperatures from 250–300°. On the other hand, it was found that the phenyl ethers were very stable toward boiling 10% hydrochloric acid or when heated alone at temperatures below decomposition.

In general, the branched chain alkyl ethers of caffeine possessed properties very similar to the straight chain compounds. However, the branched ethers were more readily converted to hydroxycaffeine by heating in dilute hydrochloric acid or heating alone at a high temperature. Evidently the substitution of alkyl groups for hydrogen on the carbon atom attached to the ethereal oxygen weakens the oxygen-carbon bond.

### Summary

1. Sixteen 8-alkyl- and aryl ethers of caffeine have been prepared, twelve of which are new compounds.

2. All of the alkyl ethers, benzyloxycaffeine and phenylethoxycaffeine are converted into hydroxycaffeine by heating in dilute hydrochloric acid or by heating alone at a high temperature. Phenyloxy- and *p*-hydroxyphenyloxycaffeine are not converted into hydroxycaffeine.

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[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

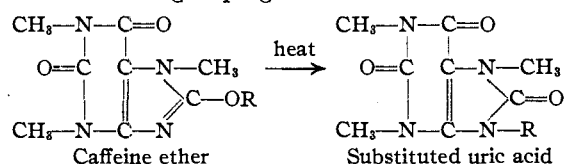
## Caffeine Derivatives. II. Molecular Rearrangement of the 8-Ethers of Caffeine

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The molecular rearrangement of the nitrogen substituted ethers has been observed by Wheeler and Johnson,<sup>2</sup> Wislicenus and Körber<sup>3</sup> and others.<sup>4</sup> It involves the transformation of the grouping  $\begin{array}{c} \text{---C---OR} \\ \parallel \\ \text{---N} \end{array}$  to  $\begin{array}{c} \text{---C=O} \\ \parallel \\ \text{---N---R} \end{array}$ .

Rearrangement of several nitrogen substituted imino ethers was found to occur most easily under the catalytic influence of an alkyl iodide but also appeared to take place by simply heating.

In the rearrangement of the 8-ethers of caffeine to the corresponding uric acids, we are dealing with the same groupings as above.



(1) Abstract from a thesis presented in partial fulfillment of the requirements for the Ph.D. degree by W. F. Allen, W. K. Kellogg Fellow at Michigan State College, 1932.

(2) Wheeler and Johnson, *Am. Chem. J.*, **21**, 185 (1899).

(3) Wislicenus and Körber, *Ber.*, **35**, 164, 1991 (1903).

(4) Wislicenus and Goldschmidt, *ibid.*, **33**, 1467 (1900); Lander, *J. Chem. Soc.*, **83**, 406 (1903).

In repeating the work of Biltz and his co-workers<sup>5</sup> on the molecular rearrangement of methoxy and ethoxycaffeine to tetramethyluric acid and trimethyl-9-ethyluric acid, respectively, it was found that the rearrangement took place fully as well, if not better, when the ethers were heated in an open tube contained in a paraffin bath. Tetramethyluric acid was obtained in yields as high as 95% (*Anal.* Calcd. for  $\text{C}_8\text{H}_{12}\text{N}_4\text{O}_8$ : N, 25.00. Found: N, 24.42.), while trimethyl-9-ethyluric acid was formed in about 50% yields (*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_8$ : N, 23.53. Found: N, 22.77).

The trimethyl-9-alkyluric acids were conveniently separated from hydroxycaffeine by forming the insoluble barium salts of the latter and extracting with chloroform.

All attempts to cause the molecular rearrangement of *n*-propyloxycaffeine to trimethyl-9-*n*-propyluric acid by heating in a closed tube were unsuccessful. However, by heating this ether in an open tube at 250–270° for eight hours, a 35% yield of trimethyl-9-*n*-propyluric acid was produced, melting at 138.8–140.6° *Anal.* Calcd. for  $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}_8 \cdot \text{H}_2\text{O}$ : N, 20.74; C, 48.88; H, 6.66. Found: N, 20.87; C, 49.20, 49.09; H, 6.40, 6.34. The properties of this compound and the method of its preparation indicate its structure. However, further proof of its configuration would be desirable, as well as the explanation of the formation of intermediate products during the pyrolysis.

(5) Biltz and Strufe, *Ann.*, **413**, 199–200 (1916–1917); Biltz and Berguis, *ibid.*, **414**, 54–57 (1917).

It was observed that a solid substance thought to be hydroxycaffeine and an oily liquid that readily vaporized were formed after the heating had been continued from two to three hours. Attempts to rearrange the secondary propyl, *n*-butyl, *n*-amyl, isoamyl and *n*-hexyl ethers were not successful.

Allyloxycaffeine, having an unsaturated alkyl group, was readily made to rearrange to the isomeric trimethyl-9-allyluric acid. A 50% yield was obtained by heating the ether in an open or closed tube at 170 to 185° for four to five hours. A small amount of hydroxycaffeine was produced at the same time.

*Anal.* Calcd. for  $C_{11}H_{14}N_4O_8$ : N, 22.40; C, 52.80; H, 5.64. Found: N, 22.42; C, 52.99; H, 5.73.

ethers. They also possessed a much more bitter taste. The crystal structure of this group showed more of a tendency toward prisms or elongated platelets than needles. All melted at higher temperatures than the ethers. All except trimethyl-9-benzyluric acid sublimed when heated above their melting points. In contrast to the original ether compounds, they were very stable toward hot dilute hydrochloric acid, but very easily decomposed by dilute alkali. All gave a pronounced murexide reaction.

It was found impossible to bring about rearrangement in the ethers having the phenyl group attached directly to the caffeine nucleus or having two carbon atoms between the benzene and caffeine nuclei.

TABLE I

PREPARATION AND PROPERTIES OF THE SUBSTITUTED URIC ACIDS OBTAINED BY THE PYROLYTIC MOLECULAR REARRANGEMENT OF THE 8-ETHERS OF CAFFEINE

8-Ethers of caffeine	G.	Conditions of heating		Open or closed tube	Rearranged compound uric acid	Crystal structure	Yield, %	M. p., °C.	
		Temp., °C.	Hrs.						
Methoxy	2	170-200	12	Closed	Tetramethyl- <sup>5</sup>	Slender needles or monoclinic prisms	35.0	225.0-226.0	
					(with $CH_3OH$ )		95.0	225.0-227.0	
Methoxy	4	240-250	4	Closed	Tetramethyl-		75.0	220.0-222.5	
Methoxy	4	225-230	5	Open	Tetramethyl-		86.0	217.0-220.4	
Methoxy	10	170-210	7	Open	Tetramethyl-		25.0	223.0-224.5	
Methoxy	2	360	15	Open	Tetramethyl-		12.5	197.0-199.0	
Ethoxy	4	240-250	10	Closed	Trimethyl-9-ethyl- <sup>5</sup>	Rectangular prisms	20.0	194.0-197.0	
					(with $C_2H_5OH$ )		44.0	199.6-202.8	
Ethoxy	5	250-260	2	Closed	Trimethyl-9-ethyl-		10.0	195.0-200.0	
Ethoxy	5	250-260	8	Closed	Trimethyl-9-ethyl-		51.2	194.0-196.0	
Ethoxy	5	240-245	2	Open	Trimethyl-9-ethyl-		7.2	136.0-138.4	
Ethoxy	5	245-255	8	Open	Trimethyl-9-ethyl-		35.5	138.8-140.6	
<i>n</i> -Propyloxy	5	245-255	8	Open	Trimethyl-9- <i>n</i> -propyl-	Needles and elongated prisms	35.0	145.0-148.0	
<i>n</i> -Propyloxy	5	250-270	10	Open	Trimethyl-9- <i>n</i> -propyl-		50.0	139.0-141.6	
Allyloxy	2	200-204	10	Closed	Trimethyl-9-allyl-	Elongated prisms	53.8	143.0-144.5	
Allyloxy	2	240-250	5	Closed	Trimethyl-9-allyl-		50.0	180.2-181.8	
Allyloxy	1.3	170-185	4	Open	Trimethyl-9-allyl-		28.0	185.0-187.5	
Benzylloxy	2	200-205	10	Closed	Trimethyl-9-benzyl-	Hexagonal platelets	20.0	187.0-189.5	
Benzylloxy	5	260-265	8	Closed	Trimethyl-9-benzyl-				
Benzylloxy	5	245-255	8	Open	Trimethyl-9-benzyl-				

Benzylloxycaffeine was made to rearrange nearly as easily as methoxycaffeine, forming the trimethyl-9-benzyluric acid. The heating was done in either an open or a closed tube at a temperature of 200 to 205° for ten hours, or at a slightly higher temperature for a shorter period. No hydroxycaffeine was produced. Not much over a 50% yield was obtained in any of the trials.

*Anal.* Calcd. for  $C_{15}H_{16}N_4O_8$ : N, 18.06; C, 60.00; H, 5.37. Found: N, 17.91; C, 59.37; H, 5.46.

The five rearranged compounds mentioned above were more soluble in water and alcohol than were their isomeric

### Summary

1. In addition to tetramethyluric acid and trimethyl-9-ethyluric acid, the following compounds have been prepared by molecular rearrangement: trimethyl-9-*n*-propyluric acid, trimethyl-9-allyluric acid and trimethyl-9-benzyluric acid.

2. It has been shown that heating the caffeine ethers alone in an open tube gave the best results. EAST LANSING, MICH. RECEIVED FEBRUARY 21, 1934